PATENT COOPERATION TREATY

PCT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
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Docket System ✓
Status Report ✓
Docket Book ✓
11/20/04 WO

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing (*day/month/year*)	20 OCT 2004
Applicant's or agent's file reference UMD-0019	REPLY DUE within 1 months/days from the above date of mailing

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US03/41136	24 December 2003 (24.12.2003)	27 December 2002 (27.12.2002)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C12Q 1/68; C12P 19/34; C07H 21/02, 21/04 and US Cl.: 435/6, 91.1, 91.2; 536/23.1, 24.3, 24.31

Applicant

UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY

1. This written opinion is the first (first, etc,) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 27 April 2005 (27.04.2005)

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Form PCT/IPEA/408 (cover sheet)(July 1998)

WRITTEN OPINION

International Application No.
PCT/US03/41136

I. Basis of the opinion

1. With regard to the elements of the international application:*

☒ the international application as originally filed

☒ the description:
pages 1-20, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 21 and 22, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-3, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-25, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE _____

☐ the claims, Nos. NONE _____

☐ the drawings, sheets/~~fig~~ NONE _____

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."*

WRITTEN OPINION

International Application No.
PCT/US03/41136

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	3, 7, 11	YES
	Claims	1, 2, 4-6, 8-10	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-11	NO
Industrial Applicability (IA)	Claims	1-11	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1, 2, 4-6, and 8-10 lack novelty under PCT Article 33(2) as being anticipated by Nazarenko. Nazarenko (see column 25) teaches a method for detecting the presence of a single nucleotide polymorphism or a mutation in a target nucleic acid wherein the method comprises: (i) amplifying a nucleic acid sequence using a hairpin primer, wherein the primer terminates at a polymorphic position; and (ii) measuring the amount of amplification product wherein a decrease in the amplification product is indicative of the presence of a polymorphism or mutation. Nazarenko (column 25) teaches that in the method of allele specific PCR, "(u)nder the appropriate reaction conditions, the target DNA is not amplified if there is a base mismatch." With respect to claims 5 and 6, Nazarenko (column 16) teaches that the hairpin primer may be DNA or RNA. With respect to claims 8-10, Nazarenk0 (column 32) teaches kits comprising the reagents necessary to perform allele specific PCR wherein the kits comprise a hairpin primer that terminates at its 3' end at the location of a single nucleotide polymorphism or mutation.

Claims 3, 7 and 11 lack an inventive step under PCT Article 33(3) as obvious over Nazarenko in view of Tyagi. The teachings of Nazarenko are presented above. With respect to claim 3, Nazarenko teaches detecting PCR amplification products at the completion of the PCR assay. Nazarenko does not teach detecting PCR products using real-time PCR. However, Tyagi teaches a method of allele specific PCR (column 3) wherein amplification products are measured either in real-time or at the end-point of the assay (column 4). Tyagi teaches that the primer used for PCR may be a hairpin primer (column 6). Tyagi (column 2) also teaches that "if the binding of the primer in the tube to the target sequence creates a mismatched 3'-terminal nucleotide, then the primer cannot be efficiently extended by incubation with DNA polymerase. Amplification of the mismatched template is significantly delayed." In view of the teachings of Tyagi, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nazarenko so as to have detected the amplification products in real-time, rather than at the completion of PCR, because Tyagi teaches that real-time PCR provides an equally effective means for monitoring allele-specific amplification.

With respect to claims 7 and 11, Nazarenko does not teach performing allele-specific PCR using hairpin primers that contain PNAs. However, Tyagi (column 6) teaches that hairpin primers used for allele specific PCR may contain PNAs. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nazarenko so as to have performed the allele-specific PCR method using hairpin primers that contain PNAs in view of the well known benefits provided by PNAs of enhancing the stability of hybridization and improving the ability to distinguish between perfectly matched and mismatched sequences. Thereby, one would have been motivated to have used PNA hairpin primers in order to have provided a more sensitive and effective method for detecting the presence of a polymorphism or mutation.

Claims 1-11 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:
The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.